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Additional ST Segment Elevation During the First Hour of Thrombolytic Therapy: An Electrocardiographic Sign Predicting a Favorable Clinical Outcome

MICHAEL SHECHTER, MD, MA, BABETH RABINOWITZ, MD, FACC, BRUNO BEKER, MD, MICHAEL MOTRO, MD, FACC, GABRIEL BARBASH, MD, MPH, ELIESER KAPLINSKY, MD, FACC, HANOCH HOD, MD

Tel-Hashomer, Israel

Objectives. The aim of this study was to investigate the significance of further ST elevation that occurs during the 1st h of thrombolytic therapy before the expected resolution.

Background. Early resolution of ST segment elevation is commonly accepted as a marker of clinical reperfusion during thrombolytic therapy for acute myocardial infarction. Using frequent electrocardiographic recordings, we observed in some patients further ST elevation that occurred during hour 1 of thrombolysis before the expected resolution.

Methods. To investigate the significance of this pattern, we classified 177 consecutive patients with a first acute myocardial infarction into two groups: Group A, 98 patients with ST elevation ≥1 mm above the initial ST elevation during the 1st h of thrombolytic therapy, and Group B, 79 patients without this finding.

Results. Although the presence or absence of additional ST elevation was not associated with a clinical or prognostic difference in patients with a first inferior or posterior acute myocardial infarction, its presence indicated a more favorable clinical outcome and prognosis in patients with anterior infarction. Among the patients with anterior infarction the 65 patients in Group A had a higher ejection fraction (44 ± 9% vs. 35 ± 11%, $p < 0.01$), less heart failure (15% vs. 35%, $p = 0.02$) and a lower in-hospital mortality rate (8% vs. 8%, $p = 0.04$) than did the 37 patients from Group B.

Conclusions. Additional ST elevation early during thrombolytic therapy in patients with anterior infarction suggests a favorable clinical outcome and thus may be indicative of successful reperfusion.

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The early resolution of ST segment elevation has become a common practical tool to assess the progress and success of thrombolytic therapy for acute myocardial infarction (1,2). However, frequently such resolution is preceded by a further transient elevation of the ST segment above the level observed at the start of thrombolytic treatment. To assess the significance, frequency and clinical implication of this phenomenon, we evaluated the behavior of the ST segment in consecutive patients with a first acute myocardial infarction who underwent thrombolytic therapy with either recombinant tissue-type plasminogen activator (rt-PA) or streptokinase. The present report summarizes the result of this evaluation.

Methods

Patients. We studied prospectively and consecutively all patients with a first acute myocardial infarction who received thrombolytic therapy in the intensive care unit of our institution during 1 year. The inclusion criteria were severe chest pain for >30 min but ≤6 h and ST segment elevation ≥0.1 mV in at least two contiguous electrocardiographic (ECG) leads. The exclusion criteria were right or left bundle branch block on the admission ECG, age >75 years, predisposition to bleeding, recent trauma, cerebrovascular accident during the past 6 months, diastolic blood pressure ≥120 mm Hg and a history of terminal illness.

Thrombolytic protocol. The patients received either rt-PA or streptokinase. A total dose of 120 mg of rt-PA was given over a 6-h infusion period that consisted of a 10-mg bolus followed by a continuous infusion of 50 mg during the 1st h, 20 mg in the 2nd h and 10 mg during each of the following 4 h. Streptokinase, 1.5 million U, was given intravenously for 1 h. Concomitantly, an intravenous bolus dose of heparin, 5,000 U, was administered and followed by continuous infusion of 25,000 IU/24 h. The heparin dose was adjusted to keep the activated partial thromboplastin at 1.5 to 2 times the baseline. Heparin infusion was continued for at least 5 days. Aspirin, 250 mg daily, was given to all patients.

Electrocardiographic analysis. A conventional three-channel (12-lead) ECG was recorded at a paper speed of

From the Heart Institute, Sheba Medical Center, Tel-Hashomer and the Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel.

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Address for correspondence: Michael Shechter, MD, MA, Heart Institute, Sheba Medical Center, 52621, Tel-Hashomer, Israel.

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Table 1. Baseline Characteristics of Patients in Group A and Group B

	Anterior Infarction (n = 102)			Inferior or Posterior Infarction (n = 75)		
	Group A	Group B	p Value	Group A	Group B	p Value
Patients	65 (64)	37 (36)		33 (44)	42 (56)	
Male	53 (82)	27 (73)	NS*	22 (67)	30 (71)	NS*
Age (yr)	60 ± 11	61 ± 10	NS†	58 ± 12	59 ± 12	NS†
Hours to treatment	2.4 ± 2.2	2.7 ± 1.3	NS†	2.5 ± 1.3	2.7 ± 1.4	NS†
Peak CK (IU)	1,250 ± 870	1,237 ± 1,159	NS†	1,109 ± 708	868 ± 494	NS†

*By chi-square test. †By Mann-Whitney rank-sum test. Data are expressed as number (%) of patients or mean value ± SD. CK = creatine kinase; Group A and Group B = patients with and without, respectively, additional ST elevation during the 1st h of thrombolytic therapy.

25 mm/s at an amplification of 10 mm/mV. Tracings were obtained on admission to the intensive care unit, at the start of thrombolytic therapy and at least every 15 min during the 1st h of treatment and every 60 min during the next 2 h. The positions of the electrodes on the chest were marked to ensure reproducibility. The isoelectric line was defined as the level of the preceding TP segment. ST segment elevation, the mean of three complexes, was measured at the J point and the lead showing the greatest ST elevation was chosen for serial analysis. Additional ST elevation was defined as ST elevation >1 mm above that recorded immediately before the start of thrombolytic therapy. All measurements were made by hand. The ECGs were reviewed without knowledge of the clinical outcome by two of the senior authors. In case of disagreement, the ECGs were evaluated by a third senior author.

Left ventricular function. All patients underwent two-dimensional echocardiography and radionuclide ventriculography (MUGA) within 48 h of admission. Two-dimensional Doppler color echocardiographic studies were performed in the traditional views. Radionuclide studies were performed with an Elscint Apex 45 digital gamma camera. A multigated equilibrium blood pool scan was performed in the anterior and 45° left anterior oblique projection with red blood cells labeled in vivo with technetium-99m (20 to 25 mCi). A left ventricular time-activity curve correlated to background was used to calculate the global ejection fraction semiautomatically. All echocardiographic studies, radionuclide examinations and left ventricular ejection fraction determinations were assessed by senior cardiologists who were unaware of the dynamic ST segment changes during the 1st h of thrombolysis or of the clinical course of the patients.

Patient evaluation. In this prospective study, all patients were examined daily by one of the senior authors and were monitored by ECG during their stay in the intensive care unit (average stay 3 days). A routine chest radiograph was performed on admission to the intensive care unit and the study was repeated when clinically indicated. Blood samples for creatine kinase (CK) were collected every 3 h during the 1st 24 h. The CK MB isoenzyme fraction was calculated from the sample in which the creatine kinase concentration was highest. Heart failure was defined clinically by presence of rales over the lungs or presence of a third sound gallop over the heart, or both, and by presence of pulmonary congestion on the chest radiograph. The protocol of this study was approved by the ethical committee (Helsinki Committee) of our institute and complies with the Department of Health and Human Services regulations for the Protection of Human Research Subjects.

Statistical analysis. Group data are expressed as mean value ±SD for continuous variables or as rates (percent) for categoric variables. Comparisons of each pair of the study subgroups (that is, patients with and without further ST segment elevation within anterior and inferior infarction subgroups) were made as follows: for continuous variables by unpaired *t* test and by Mann-Whitney rank-sum test. Categoric variables were compared by chi-square statistic and the Fisher exact test when appropriate.

Results

Patient data at baseline. A total of 221 patients with acute myocardial infarction were admitted to the intensive care unit and received thrombolytic therapy. Excluded from the study were 44 patients with a history of previous myocardial infarction or complete bundle branch block on admission ECG. Finally, 177 patients (133 male and 44 female) with a first acute myocardial infarction were included in the study (Table 1): 102 patients had an anterior infarction and 75 had a posterior or inferior infarction. Streptokinase was given to 143 patients (81%) and rt-PA to 34 (19%). The patients were classified into two groups: Group A, 98 patients (65 with anterior and with 33 inferior or posterior infarction) who exhibited additional ST elevation (Fig. 1), and Group B, 79 patients (33 with anterior and 42 with inferior or posterior infarction) without further ST elevation.

The two groups received the same adjuvant therapy in the intensive care unit (beta-adrenergic blocking agents, nitrates, aspirin and calcium channel antagonists). The two groups were comparable in relation to age, gender and interval from the onset of chest pain to initiation of thrombolytic treatment (Table 1). The groups did not differ significantly in infarct site (anterior or inferoposterior) and a comparable proportion had risk factors of coronary artery disease (hypertension, cigarette smoking, obesity, hyperlip-

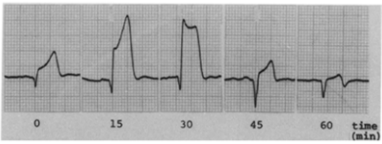

Figure 1. Tracing (lead V_3) from a patient with anterior infarction in Group A (patients with additional ST segment elevation in the 1st h of thrombolytic therapy). Fifteen minutes after the initiation of therapy, the ST segment elevated further, reaching a maximal height 30 min after the start of treatment and then decreasing in height.

idemia, diabetes mellitus), angina pectoris and congestive heart failure before hospital admission.

ST elevation after thrombolytic therapy. In patients with anterior infarction from Group A, additional ST elevations were recorded mostly in leads V_3 to V_4. Ninety percent of patients from Group A demonstrated additional ST segment elevation within 30 min from initiation of thrombolytic therapy; of these, 61 patients (62%) demonstrated ST elevation 15 min after treatment, 24 patients (25%) after 30 min, 8 patients (8%) after 45 min and 5 patients (5%) after 60 min. In Group A, 29 patients (30%) had additional ST elevation of 1 mm, 35 patients (36%) of 2 mm, 13 patients (13%) of 3 mm, 8 patients (8%) of 4 mm and 13 patients (13%) >4 mm. The maximal additional ST segment elevation was seen 30 min after initiation of thrombolytic therapy. The additional ST segment elevation continued at least 10 to 15 min in most of the patients from Group A.

Clinical signs of reperfusion. There was at least a 50% reduction in ST segment elevation 1 h after treatment in 56% of patients from Group A (55 of 98 patients) and in 63% from Group B (50 of 79 patients).

In 72% of patients from Group A and 29% from Group B, chest pain was reduced to 50% of its maximal level within 1 h from initiation of treatment. In 74% of Group A patients with anterior infarction and in 50% of Group B patients with anterior infarction, chest pain decreased to 50% of maximal level within 1 h.

Myocardial enzyme kinetics. Groups A and B were comparable with regard to CK levels (Table 1); nonetheless, the time from the start of chest pain to peak CK level was shorter in patients with anterior infarction from Group A than in those from Group B (10.5 ± 4.7 vs. 13.4 ± 8.2 h, respectively, $p = 0.02$) (Table 2) and almost identical in patients with inferior or posterior infarction from Group A and Group B (12.8 ± 5.4 vs. 13.6 ± 5.7 h, respectively, $p = 0.53$). The time from the start of thrombolytic therapy to peak CK level was significantly shorter in patients with anterior infarction from Group A than in those from Group B (7.5 ± 4.4 vs. 11.3 ± 8.0 h, respectively, $p < 0.01$) and almost identical in patients with inferior or posterior infarction from Groups A and B (10.2 ± 4.6 vs. 11.2 ± 5.9 h, respectively, $p = 0.65$).

Congestive heart failure and mortality. Although the presence or absence of additional ST elevation was not associated with better clinical outcome in patients with a first inferior or posterior infarction, further ST elevation indicated a more favorable clinical outcome in patients with anterior infarction (Table 2). Thus, patients with anterior infarction from Group A (with additional ST elevation) had better preserved left ventricular function with a higher left ventricular ejection fraction (44 ± 9% vs. 35 ± 11%, $p < 0.01$), less heart failure (15% vs. 8%, $p = 0.02$) and a lower in-hospital mortality rate (0% vs. 8%, $p = 0.04$) than did patients with anterior infarction from Group B. Four patients, all from Group B (three with anterior infarction) died in the hospital: two from ventricular rupture and two from cardiogenic shock.

Other complications. There were no significant differences in the incidence of left ventricular thrombus formation or the occurrence of major ventricular arrhythmias, conduction disturbances and postmyocardial infarction angina in the two groups (Table 2).

Table 2. Clinical Outcome in Patients With and Without Additional ST Elevation

	Anterior Infarction (n = 102)			Inferior or Posterior Infarction (n = 75)		
	Group A n = 65	Group B n = 37	p Value	Group A n = 33	Group B n = 42	p Value
Hours to peak CK	7.5 ± 4.4	11.3 ± 8.0	<0.01*	10.2 ± 4.6	11.2 ± 5.9	NS*
Hours from pain to peak CK	10.5 ± 4.7	13.4 ± 8.2	0.02*	12.8 ± 5.4	13.6 ± 5.7	NS*
LVEF (%)	44 ± 9	35 ± 11	<0.01*	50 ± 11	51 ± 8	NS*
Heart failure	10 (15)	13 (35)	0.02†	3 (6)	3 (7)	NS†
Left ventricular thrombus	10 (15)	7 (19)	NS†	1 (3)	1 (2)	NS†
Conduction disturbances	8 (12)	6 (16)	NS†	4 (12)	4 (10)	NS†
VPCs	12 (18)	9 (24)	NS†	6 (18)	8 (19)	NS†
Postinfarction angina	12 (18)	8 (12)	NS†	8 (24)	8 (19)	NS†
In-hospital mortality	—	3 (8)	0.04†	—	1 (2)	NS†

*By one-way analysis of variance (ANOVA) test. †By Fisher exact test. Data are expressed as mean value ± SD or number (%) of patients. LVEF = left ventricular ejection fraction; VPCs = ventricular premature complexes (Lown grade 2 to 5); other abbreviations as in Table 1.

Discussion

Noninvasive and invasive markers of reperfusion. Thrombolytic treatment in acute myocardial infarction has been shown to be effective in preserving the left ventricular function (3) and in reducing short- and long-term mortality (4,5). Nevertheless, reperfusion is successful in only 60% to 70% of treated patients (6). The "nonresponders" have a significantly higher mortality rate (7,8) and may therefore be candidates for emergency angioplasty or coronary artery bypass surgery.

Simple and rapid noninvasive methods for determining reperfusion may be helpful in evaluating the efficacy of thrombolytic treatment and enable early recognition of patients who will respond favorably to thrombolytic therapy and those who will not. Some noninvasive markers used to predict reperfusion are a rapid reduction in ST segment elevation (1,2), relief from chest pain (9), early peak of serum CK levels (10), reperfusion arrhythmias (11) and early inversion of T waves (12).

Although coronary angiography immediately after treatment is the most accurate way to document coronary artery patency, it is rarely indicated for that purpose alone. Prediction of successful thrombolytic treatment from CK curves allows only a retrospective diagnosis of reperfusion. It has been suggested that analysis of the ST segment by single or multiple ECG leads is useful, but there is no consensus about the degree of reduction in ST segment elevation needed to predict reperfusion because different techniques and criteria have been used (2,13–15). From the data presented here, the additional ST elevation during the 1st h of thrombolytic therapy may become yet another indicator for successful outcome.

ST segment elevation as a marker of reperfusion. Sato et al. (16) used intracoronary urokinase infusion for patients with acute myocardial infarction and found that in 13 of 16 patients with an occluded left anterior descending coronary artery, additional ST elevation occurred abruptly 5 min after recanalization of the occluded artery. However, the small number of patients in that study precluded definite conclusions. Kwon et al. (17) reported the only other study describing further ST segment elevation. They followed up 31 patients with acute myocardial infarction who received thrombolytic therapy with continuous ECG monitoring and found, in almost one third of the patients, delayed, transient and sustained recurrences of ST elevation after an initial early rapid resolution (<3 h) after intravenous thrombolysis. Transient recurrent ST elevation was associated with a delayed time to peak creatine kinase and sustained recurrence was associated with reduced late arterial patency and angiographic perfusion scores and worse residual stenosis. Kwon and coworkers (17) assumed that the cause of the recurrent ST elevation was reocclusion of the infarct-related artery. Although their result seems to contradict ours, the phenomenon was defined within the 1st 60 min of thrombolysis in our study, whereas Kwon et al. may indeed have observed a delayed reocclusion after an initial successful reperfusion.

ST elevation in patients with anterior versus inferior or posterior infarction. We found that more than half of the patients with a first acute myocardial infarction (and two thirds of patients with an anterior wall infarct site) who received thrombolytic treatment demonstrated additional ST elevation during the 1st h of thrombolysis. Although this ECG development did not appear to predict a particular clinical course in patients with a first inferior or posterior acute myocardial infarction, it was associated with a better clinical outcome and prognosis in patients with anterior infarction. Thus, preservation of left ventricular function, as measured by left ventricular ejection fraction, was better in patients with a first anterior infarction who demonstrated further ST elevation than in patients without this finding.

In addition, all patients with a first anterior acute myocardial infarction who demonstrated further ST elevation survived the hospital stay, whereas four patients without this pattern died in the hospital ($p = 0.04$). The finding that the additional ST elevation did not predict a better clinical outcome in patients with a posterior or inferior infarction is in accord with the general difficulty in proving the benefit of thrombolytic therapy in these patients.

Possible mechanisms. The mechanism of this additional ST elevation during the 1st h of thrombolysis remains unclear. Whether the metabolic change (transient high potassium concentration in the extracellular fluid [18]) in the reperfused ischemic myocardium is responsible for this ECG pattern, whether it occurs by spasm or distal embolization during thrombus dislodgment or whether it is a sign of reperfusion injury remains to be elucidated. Our findings encourage further studies to understand this unique observation.

Conclusions. Our data suggest that the ECG pattern of additional ST elevation in the 1st h of thrombolytic therapy is a simple and rapid noninvasive method for recognizing patients with a first anterior acute myocardial infarction who respond favorably to thrombolytic therapy and have a better clinical outcome.

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